REMARKS

Background and Prosecution to Date

The present invention is based on Applicants' discovery that the combined administration of an anti-angiogenic agent (presently a VEGF receptor tyrosine kinase inhibitor) and a Src kinase inhibitor provides an improved anti-cancer or anti-tumor effect *and additionally* that the Src kinase inhibitor at least in part counterbalances the blood pressure rise that follows administration of the anti-angiogenic agent. This dual effect of the combination is clearly set forth in the present claims.

Pursuant to a restriction requirement, the elected *method of treating cancer* invention is directed toward a method of producing an anti-cancer effect (independent claim 13) and a method of treatment of a solid tumor disease (independent claim 23). Claims 24-27 are dependent on method claims 13 and/or 23, with claims 24-26 being directed toward specific types of cancers and claim 27 being directed toward the simultaneous, sequential or separate administration of the two components of the combination. Pursuant to a provisional requirement for election of a "single disclosed disease associated with angiogenesis," Applicants elected lung cancer as the *disease* species.

At the time of the present Action, independent claims 13 and 23 recited three specific compounds from which the VEGF receptor tyrosine kinase inhibitor is selected and three specific compounds from which the Src kinase inhibitor is selected. Claims 14-22 (dependent on claim 13) were each directed toward various single combinations of VEGF receptor tyrosine kinase inhibitor and Src kinase inhibitor selected from the specific compounds recited in claim 13. Pursuant to a provisional requirement for election of a specific VEGF receptor tyrosine kinase inhibitor and a specific Src kinase inhibitor, Applicants elected as the VEGF receptor tyrosine kinase inhibitor species the compound 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (hereinafter sometimes referred to as "**VTK-1**"), and as the Src kinase inhibitor species the compound 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(6-chloro-2,3-methylenedioxyanilino)-5-isopropoxyquinazoline (hereinafter sometimes referred to as "**Src-1**").

Claim Amendments

In a further effort to expedite the prosecution of this application toward allowance, specific combination claims 17 and 19-22 have been cancelled above so as to focus the claimed invention on the specific combinations of dependent claims 14, 15, 16 and 18. As will be discussed further below, claims 14, 15, 16 and 18 are directed toward particular combinations that are specifically described in the specification in sufficient detail that the skilled person would clearly be able to practice and achieve the objective of the claimed method. Consistent therewith, independent claims 13 and 23 have been amended to list only those compounds used in the specific combinations recited in claims 14, 15, 16 and 18. Moreover, as detailed further below, verification that one of ordinary skill in the art could use the claimed method to treat lung cancer with a reasonable expectation of success is provided by way of the Declaration of Dr. Paul Elvin (hereinafter "the Elvin Declaration"), which establishes that each of the anti-angiogenic components (the VEGF receptor tyrosine inhibitors) recited in every claim, when separately tested, demonstrates at least a moderate level of inhibition using solid tumors grown from the human lung cancer cell line CaLu-6. The Elvin Declaration additionally demonstrates the superior efficacy of three presently claimed combinations of VEGF receptor tyrosine kinase inhibitors and Src kinase inhibitors, relative to the individual components alone, in the inhibition of CaLu-6 tumors.

Claims 13 and 23 have also been amended to refer to plural salts, consistent with the "selected from" format of these claims, and 14, 15, 16 and 18 have been amended to more appropriately refer to "the" method according to claim 13.

It should be clear from the above that no new matter has been added by these amendments, and entry thereof is believed to be appropriate and is respectfully requested. All claim amendments that have been made in this application are without disclaimer or prejudice to Applicants' right to prosecute any subject matter deleted thereby in one or more divisional or continuing applications.

Following entry of these amendments, claims 13-16, 18 and 23-27 remain pending in this application, with claims 14-16 being indicated as "withdrawn" pursuant to the Examiner's position in the current Action.

Withdrawal of Claims from Consideration

The Examiner has withdrawn claims 14-17 and 19-22 from further consideration as being drawn to a nonelected species, there being no allowable generic or linking claim. In order to advance the prosecution of this application, claims 17 and 19-22 have been cancelled. However, it is believed that the above amendments and the following remarks, supported by the Elvin Declaration, establish that *all* of remaining claims 13-16, 18 and 23-27 are enabled and allowable, and therefore reconsideration and rejoinder of claims 14-16 in this application are believed to be in order and are respectfully requested.

Claim Rejections - 35 USC § 112

Claims 13, 18 and 23-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. These claims are said to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner asserts that the claims are drawn to a method of treating lung cancer, but that the prior art indicates that lung cancer is difficult to treat. In support the Examiner cites Oxford Textbook of Oncology, p. 451, Table 3 as reporting that squamous cell lung cancer and adenocarcinoma of the lung are highly resistant to chemotherapy, and these negative results indicate a lack of predictability in the art. The Examiner further asserts that "Applicants have provided no working examples demonstrating the efficacy of this treatment on any cancer, but only data that demonstrates the normotensive effect of the treatment." From this the Examiner concludes that "it would take undue experimentation by one of ordinary skill in the art to use this method to treat lung cancer with a reasonable expectation of success."

This ground for rejection is respectfully traversed on the basis of the following evidence and argument, which demonstrate that the specification fully enables the skilled person to practice the invention of all presently pending claims (whether or not designated as withdrawn) without undue experimentation and with a reasonable expectation of success.

It is thus understood that the Examiner has acknowledged in the rejection that data in the specification demonstrates the normotensive effect of the treatment of the claims under consideration (claims 13, 18 and 23-27), but bases this non-enablement rejection on the lung cancer treatment aspect of the claimed dual effect treatment. It is respectfully submitted that the

attached Elvin Declaration confirms the efficacy of *each* of the anti-angiogenic components (each VEGF receptor tyrosine kinase inhibitor) recited in every combination now claimed, including the specific combinations of withdrawn claims 14, 15 and 16. Moreover, the Elvin Declaration demonstrates that three examples of specific VEGF receptor tyrosine kinase inhibitor/Src kinase inhibitor combinations provide significantly more effective inhibition in the lung cancer model than the individual components when administered alone.

First of all, the specification particularly discloses the combinations of the VEGF receptor tyrosine kinase inhibitors and Src kinase inhibitors that are recited in the present method claims, including disclosure of preferred doses for the oral administration of the components of such combinations, as well as the cancers (including lung cancer) that are amenable to this treatment.

Thus, the particular combinations recited in the present method claims 14, 15, 16 and 18 are specifically described in the specification as filed, *inter alia*:

(i) the combination recited in claim 14 is described in the text on page 50, line 30, to page 51, line 13, being

- the VEGF receptor tyrosine kinase inhibitor 4-(4-fluoro-2-methylindo1-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-ylpropoxy)quinazoline (hereinafter sometimes referred to as "**AZD2171**"), and
- the Src kinase inhibitor 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (hereinafter sometimes referred to as "**AZD0530**");

(ii) the combination recited in claim 15 is described in the text on page 49, at lines 25 to 31, being

- the VEGF receptor tyrosine kinase inhibitor 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (hereinafter sometimes referred to as "**VTK-1**") and
- the Src kinase inhibitor **AZD0530**;

(iii) the combination recited in claim 16 is described in the text on page 50, at lines 11 to 17, being

- the VEGF receptor tyrosine kinase inhibitor 4-(4-bromo-2-fluoroanilino)-6-

methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (**ZD6474**); and

- the Src kinase inhibitor **AZD0530**; and

(iv) the combination recited in claim 18 is described in the text on page 49, at lines 19 to 24, being

- the VEGF receptor tyrosine kinase inhibitor **VTK-1**, and
- the Src kinase inhibitor 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(6-chloro-2,3-methylenedioxyanilino)-5-isopropoxyquinazoline (hereinafter sometimes referred to as "**Src-1**").

Moreover, independent claims 13 and 23 as amended recite *only* the three VEGF receptor tyrosine kinase inhibitors (AZD2171, VTK-1 and ZD6474) and the two Src kinase inhibitors (AZD0530 and Src-1) of the specific combinations recited in claims 14, 15, 16 and 18.

Preferred doses for oral administration of the anti-angiogenic component of the claimed combinations (now restricted to three particular VEGF receptor tyrosine kinase inhibitors) are provided on page 45, at lines 16 to 19. Preferred doses for oral administration of the Src kinase inhibitor component of the claimed combinations are provided on page 45, at lines 26 to 29.

Cancers treatable by the method of the invention (including lung cancer) are disclosed in the specification on page 9, at lines 26 to 32, with solid tumors being disclosed on page 8, at lines 10 to 12, and on page 10, at lines 1 and 2.

Thus, it is respectfully submitted that the specification as filed provides one of ordinary skill in the art with sufficient information to carry out the presently claimed methods, particularly considering the more limited scope of the components recited in the presently claimed methods, and based on this disclosure such person would have a reasonable expectation of success in the treatment of various cancers, including lung cancer.

Confirmation of this reasonable expectation of success to treat lung cancer is provided by way of the Elvin Declaration wherein it is demonstrated, using solid tumors grown from the human lung cancer cell line CaLu-6, that the combination of VEGF receptor tyrosine kinase inhibitors with the Src kinase inhibitor AZD0530 as recited in present claims 14, 15 and 16 provided a statistically significant increase in the inhibition of tumor growth compared to that which was achievable on dosing each compound alone.

Thus, the test described in the Elvin Declaration measured the ability of a combination

product of the invention to inhibit the growth of human CaLu-6 lung cancer cells (ATCC Cat. No. HT13-56) grown as xenograft tumors in athymic nude mice.

CaLu-6 tumor xenografts were established in the flank of female athymic Swiss *nu/nu* mice, by subcutaneous injection of $1x10^6$ CaLu-6 cells/mouse in 100 µl of a 50% (v/v) solution of Matrigel (Beckton Dickinson Catalogue No, 40234) in serum free culture medium (Eagle's Minimum Essential Medium, Gibco Catalogue No 21090-022). Ten days after cellular implant, mice were allocated to groups of 8-10 animals having comparable group mean tumor volumes. Treatment was commenced on day 10 with either a single agent or agents in combination being administered orally once daily for a minimum of 21 days, usually for about 28 days. Each single agent or combination product was prepared as a ball-milled suspension in 1% polysorbate-80 vehicle and dosed at 0.1ml/10g body weight at the appropriate dose.

Control animals received compound diluent only. Tumors were measured twice weekly, using vernier calipers and volumes were calculated using the formula

$$(l \times w) \times \sqrt{(l \times w)} \times (\pi/6)$$

where l is the longest diameter and w the diameter perpendicular to the longest. The level of growth inhibition was calculated by comparison of the geometric mean tumor volume of the control group versus the treatment group using a Student's T test.

The following combinations of VEGF receptor tyrosine kinase inhibitors and Src kinase inhibitors were tested in the CaLu-6 tumor xenograft model:

(i) the VEGF receptor tyrosine kinase inhibitor 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-piperidinopropoxy)quinazoline (**VTK-1**);

and the Src kinase inhibitor 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (**AZD0530**);

(ii) the VEGF receptor tyrosine kinase inhibitor 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (**ZD6474**);

and the Src kinase inhibitor **AZD0530**; and

(iii) the VEGF receptor tyrosine kinase inhibitor 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-(pyrrolidin-1-ylpropoxy)quinazoline (**AZD2171**);

and the Src kinase inhibitor **AZD0530**.

VTK-1 is amongst the VEGF receptor tyrosine kinase inhibitors listed in current claim 13

and AZD0530 is amongst the Src kinase inhibitors also listed in that claim. The particular combination of VTK-1 and AZD0530 is described in the specification on page 49, at lines 25 to 31, and this particular combination is claimed in current claim 15.

ZD6474 is amongst the VEGF receptor tyrosine kinase inhibitors listed in current claim 13 and AZD0530 is amongst the Src kinase inhibitors also listed in that claim. The particular combination of ZD6474 and AZD0530 is described in the specification on page 50, at lines 11 to 17, and this particular combination is claimed in current claim 16.

AZD2171 is amongst the VEGF receptor tyrosine kinase inhibitors listed in current claim 13 and AZD0530 is amongst the Src kinase inhibitors also listed in that claim. The particular combination of AZD2171 and AZD0530 is described in the description on page 50, line 30, to page 51, line 3, and this particular combination is claimed in current claim 14.

The data in Figures 4, 5 and 6 of the Elvin Declaration show that, in each case, each VEGF receptor tyrosine kinase inhibitor and each Src kinase inhibitor demonstrated activity in the CaLu-6 lung cancer model when dosed alone, but that each combination of a VEGF receptor tyrosine kinase inhibitor with a Src kinase inhibitor demonstrated a markedly enhanced anti-tumor effect.

Figure 4 shows the results of an experiment involving the VEGF receptor tyrosine kinase inhibitor VTK-1 and the Src kinase inhibitor AZD0530. Treated animals received either VTK-1 dosed at 3 mg per kg p.o. or AZD0530, 50 mg per kg p.o. as single agents. In order to deliver a combined treatment, appropriate weights of the two agents were ball-milled together in 1% polysorbate-80 to provide suspensions such that a single p.o. dose delivered VTK-1 at 3 mg per kg plus AZD0530 at 50 mg per kg. Treatment was continued for 28 days and control animals received 1% polysorbate-80 vehicle only, 0.1ml/10g p.o once daily for 28 days.

Both VTK-1 and AZD0530 alone inhibited CaLu-6 tumor growth compared to vehicle treated controls, Treatment with VTK-1 alone resulted in a moderate inhibition of CaLu-6 tumor growth of about 39% compared to control animals after 21 days treatment. AZD0530 alone inhibited tumor growth by about 51% after 21 days treatment. In contrast, after 21 days treatment the combination of VTK-1 at 3 mg per kg with AZD0530 at 50 mg per kg inhibited tumor growth by about 70% compared to controls. Combination of VTK-1 with AZD0530 was **significantly more effective** when compared to VTK-1 alone (**$p<0.001$**). Combination treatment

was similarly **significantly more effective** when compared to AZD0530 alone (**p<0.001**).

It can be seen from the graphs in Figure 4 that, after 28 treatment days, the beneficial effect of the combination treatment compared to the individual treatments was increased.

Figure 5 shows the results of an experiment involving the VEGF receptor tyrosine kinase inhibitor ZD6474 and the Src kinase inhibitor AZD0530. Treated animals received either ZD6474 dosed at 25 mg per kg p.o. or AZD0530 dosed at 50 mg per kg p.o., single agents.

In order to deliver a combined treatment, appropriate weights of the two agents were ball-milled together in 1% polysorbate-80 to provide suspensions such that a single p.o.dose delivered ZD6474 at 25 mg per kg plus AZD0530 at 50 mg per kg,

Both ZD6474 and AZD0530 alone resulted in a moderate inhibition of CaLu-6 tumor growth of about 50% compared to vehicle treated controls. In contrast, combination treatment of ZD6474 at 25 mg per kg with AZD0530 at 50 mg per kg provided markedly greater inhibition of tumor growth of about 79%. Combination of ZD6474 with AZD0530 was **significantly more effective** when compared to ZD6474 alone (**p<0.001**). Combination treatment was similarly **significantly more effective** when compared to AZD0530 alone (**p<0.001**).

Figure 6 shows the results of an experiment involving the VEGF receptor tyrosine kinase inhibitor AZD2171 and the Src kinase inhibitor AZD0530. Treated animals received either AZD2171 dosed at 3 mg per kg p.o, or AZD0530 dosed at 50 mg per kg p.o., as single agents. In order to deliver a combined treatment, appropriate weights of the two agents were ball-milled together in 1% polysorbate-80 to provide suspensions such that a single p.o. dose delivered AZD2171 at 3 mg per kg plus AZD0530 at 50 mg per kg.

Both AZD2171 and AZD0530 alone resulted in a moderate inhibition of CaLu-6 tumor growth of about 55% compared to vehicle treated controls. In contrast, combination treatment of AZD2171 at 3 mg per kg with AZD0530 at 50 mg per kg provided markedly greater inhibition of tumor growth of about 76%. Combination of AZD2171 with AZD0530 was **significantly more effective** when compared to AZD2171 alone (**p<0.001**). Combination treatment was similarly **significantly more effective** when compared to AZD0530 alone (**p<0.001**).

Therefore, with respect to the present enablement rejection the Elvin Declaration demonstrates that *each* of the anti-angiogenic components (VEGF receptor tyrosine kinase inhibitors AZD2171, VTK-1 and ZD6474) recited in *all* claims when separately tested

demonstrates at least a moderate inhibition of CaLu-6 tumor. It is therefore respectfully submitted that the Examiner's assertion that "it would take undue experimentation by one of ordinary skill in the art to use this method to treat lung cancer with a reasonable expectation of success" has clearly and directly been overcome with respect to all of claims 13, 18 and 23-27 under consideration *and also* withdrawn claim 14, 15 and 16, each of which recites only the anti-angiogenic components for which efficacy in lung cancer has been demonstrated.

Moreover, the *specific* combinations of VEGF receptor tyrosine kinase inhibitors and Src kinase inhibitors of withdrawn claim 14, 15 and 16 have been demonstrated by the Elvin Declaration to be significantly more effective when compared to the individual components when used alone.

Accordingly, it has been demonstrated by evidence in the specification and supporting evidence in the Elvin Declaration that the claimed method for the production of an anti-cancer or anti-tumor effect comprising the administration of combinations of a particular VEGF receptor tyrosine kinase inhibitor (selected from a list of three possibilities) with a particular Src kinase inhibitor (selected from a list of just two possibilities) provides an improved anti-cancer or anti-tumor effect and that an appropriate dose of each component can be selected such that their contrasting blood pressure effects can be substantially counter-balanced. It is therefore believed that the lack of enablement rejection has been overcome, and withdrawal of this rejection is respectfully requested.

Information Disclosure Statement

The Examiner's attention is called to the further Information Disclosure Statement submitted herewith, citing a Poster presented in late May/early June 2008 at the recent ASCO Meeting in Chicago. The Poster is entitled "A Phase I, open-label, multicenter study of cediranib and AZD0530 in patients with advanced solid tumors" presented by Trarbach *et al.* Cediranib is also known as AZD2171. Due to the constraints of electronic filing with the US Patent and Trademark Office, is it not possible to submit a full size copy of this Poster in its original color. Therefore, a 8-½ x 11 copy of the full poster is being provided, as well as a larger (more legible) copy is being provided with each half of the Poster being submitted on one of two 8-½ x 11 inch sheets. This Information Disclosure Statement additionally lists the published applications noted below.

Technically Related Pending Applications of Applicant's Assignee

The Examiner's attention is called to the following Tables of pending U.S. applications of Applicant's assignee that may be considered technically related to the present invention insofar as they each claim combination therapy involving one of the VEGF receptor tyrosine kinase inhibitors or one of the Src kinase inhibitors recited in the present claims together with another different therapeutic agent.

The following Table lists technically related pending U.S. applications of Applicants' assignee that claim a combination of ZD6474 with another therapeutic agent identified under the heading "Combination with." The current status of each application as reported in the PAIR database is given in the right-hand column. Each of the published US applications and PCT applications is listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of each listed published PCT application is provided with the Information Disclosure Statement.

It is assumed that the Examiner has ready electronic access to each of the listed US applications, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

US Appln	Date US Filed	US Pub. #	PCT Pub. #	Combination with	Current Status
10/240413	01-Oct-2002	US 2003-0144298	WO2001/74360	Anti-hypertensive	Pending before Examiner Rae, GAU 1611; Final Rejection Mailed October 2, 2008
10/494704	19-Oct-2004	US 2005-0043395	WO2003/039551	Taxane	Pending before Examiner Pagonaksis, GAU 1614; Final rejection mailed August 25, 2008
10/543106	22-Jul-2005	US 2006-0142316	WO2004/071397	5-FU/CPT-11	Pending before Examiner Stone, GAU 1614; Final rejection mailed July 22, 2008
10/523832	08-Feb-2005	US 2005-0222183	WO2004/014383	radiotherapy	Pending before Examiner Stone, GAU 1614; Final rejection mailed July 11, 2008
10/523838	08-Feb-2005	US 2005-0245549	WO2004/014426	Iressa (ZD1839)	Pending before Examiner Stone, GAU 1614; Final rejection mailed July 9, 2008
10/530567	07-Apr-2005	US 2006-0009418A1	WO2004/032937	Gemcitabine	Pending before Examiner Finn, GAU 1614; Final Rejection Mailed September 15, 2008
10/536668	27-Aug-2005	US 2006-0167027	WO2005/004870	Platinum	Pending before Examiner Khanna, GAU 2151; Response to restriction requirement filed October 3, 2008

US Appln	Date US Filed	US Pub. #	PCT Pub. #	Combination with	Current Status
11/663913	27-Mar-2007	US 2008-0119479	WO2006/035204	Imatinib	Pending before Examiner Pagonaksis, GAU 1614; Restriction requirement mailed September 8, 2008
11/666762	12-Dec-2007	US 2008-0200436	WO2006/048633	Anti-androgen	Pending before Examiner Pagonaksis, GAU 1614; Response to restriction requirement mailed October 6, 2008
12/158264	19-Jun-2008	--	WO2007/071958	pemetrexed	Pending before Examiner Pagonaksis, GAU 1614; Restriction Requirement mailed September 30, 2008

The following Table lists technically related pending U.S. applications of Applicants' assignee that claim a combination of AZD2171 with another therapeutic agent identified under the heading "Combination with." The current status of each application as reported in the PAIR database is given in the right-hand column. Each published US applications and PCT application is listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of the listed published PCT application is provided with the Information Disclosure Statement.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

US Appln	Date US Filed	US Pub. #	PCT Pub. #	Combination with	Current Status
10/240,413	01 Oct 2002	US 2003 0144298	WO 2001/74360	Anti-hypertensive	Assigned to Examiner Charlesworth E Rae in GAU 1611; Final Rejection Mailed 10-02-2008
10/563,440	05 Jan 2006	US 2006 0160775	WO 2005/004871	ZD6126	Assigned to Examiner Chris E Simmons in GAU 1612; Final Rejection Mailed 07-22-2008
10/563,439	05 Jan 2006	US 2006-0167024	WO 2005/004872	ZD1839	Assigned to Examiner Benjamin J Packard in GAU 1612; Non Final Action Mailed 09-10-2008
10/594,233	25 Sep 2006	US 2006-0125447	WO 2005/092303	CPT-11 and/or 5-FU	Assigned to Examiner Shyam Nathan in GAU 4161; restriction requirement mailed 11-Aug-2008
10/594,234	25 Sep 2006	US 2007 0135462	WO 2005/092385	Taxane. optionally IR	Assigned to Examiner Charlesworth E Rae in GAU 1611; Non Final Action Mailed 06-19-2008

US Appln	Date US Filed	US Pub. #	PCT Pub. #	Combination with	Current Status
10/594,235	25 Sep 2006	US 2008 0113039	WO 2005/092384	Platinum anti-tumour agent, optionally IR	Assigned to Examiner Shyam Nathan in GAU 4161; Non Final Action Mailed 10-03-2008
11/663,912	27 Mar 2007	US 2008 0015205	WO 2006/035203	Imatinib [Gleevec]	Assigned to Examiner James D. Anderson in GAU 1614; Non Final Action Mailed 09-22-2008
11/994,824	04 Jan 2008		WO 2007/003933	Gemcitabine [Gemzar]	Application Undergoing Preexam Processing; Not yet assigned or published
12/158,266	19 Jun 2008		WO 2007/071970	pemetrexed	Assigned to GAU 1614, no Examiner assigned; predicted first Action 36 months.

The following Table lists technically related pending U.S. applications of Applicants' assignee that claim a combination of the Src kinase inhibitors AZD0530 and/or Src-1 with another therapeutic agent identified under the heading "Combination with." The current status of these applications as reported in the PAIR database is given in the right-hand column. Each published US applications and PCT application is listed on the form PTO-1449 attached to the Information Disclosure Statement being submitted herewith, and a copy of the listed published PCT application is provided with the Information Disclosure Statement.

Again, it is assumed that the Examiner has ready electronic access to this pending US application, but the undersigned will provide a copy of any document from these files if requested by the Examiner.

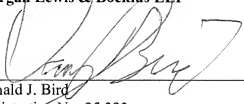
US Appln	Date US Filed	US Pub. #	PCT Pub. #	Combination with	Current Status
10/534,721	20-Oct-2005	US 2006-0142297	WO2004/043472	gemcitabine	Pending before Examiner Zarek, GAU 4161; Non-final rejection mailed May 28, 2008.
11/577,940	29-Nov-2006	US 2007-0254893	WO2005/117888	antioestrogen, EGFR TKI	Pending before Examiner Yong Soo Chong, GAU 1617; predicted first Action 14 months

Conclusion

All grounds for rejection having been addressed, and it is believed overcome by the above amendment and the foregoing remarks supported by the Elvin Declaration, reconsideration of the withdrawal of claims 14, 15 and 16 and the allowance of all of claims 13-16, 18 and 23-27 is believed to be in order and is respectfully requested.

Except for issue fees payable under 37 C.F.R. §1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP



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